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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/753,289	01/05/2004	Steven M. Watkins	475512000100	1703

25226 7590 12/18/2006
MORRISON & FOERSTER LLP
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EXAMINER	
NEGIN, RUSSELL SCOTT	

ART UNIT	PAPER NUMBER
1631	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	12/18/2006	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

TH

Office Action Summary	Application No. 10/753,289	Applicant(s) WATKINS, STEVEN M.	
	Examiner Russell S. Negin	Art Unit 1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.
- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 29 September 2006.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 2-19 and 54-57 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 2-19 and 54-57 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____ 11/14/06 3/29/06 8/22/05 1/15/04 1/5/04
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group I in the reply filed on 29 September 2006 is acknowledged.

Applicant's election without traverse of the following five species in the reply filed on 29 September 2006 is acknowledged.

Category #1: 5, 8,11 eicosatrienoic acid & 5,8,11,14,17-eicosapentaenoic acid

Category #2: 18:2n6

Category #3: 5-cholesten-3b-ol

Category #4: cardiolipin

Category #5: dipentadecaenoyl phosphatidylethanolamine

It is acknowledged that claim 1 is cancelled.

It is acknowledged that claims 54-57 are added.

It is also acknowledged that claims drawn to the non-elected group, claims 20-53, are cancelled.

Claims 2-19 and 54-57 are examined in this Office action.

Information Disclosure Statement

The Information Disclosure Statement filed on 29 March 2006 does not contain a legible copy of each reference listed on the list of references. It is not known whether this is an error of the applicants or a scanning error by the Office. Consequently the

missing references have been listed as not considered in the signed copy of the list of references attached to this Office action. If the applicants provide a legible copy of the missing references in response to this Office action, the references will be considered under 37 CFR 1.97(f), and a signed copy of the list of references indicating consideration of the missing references will be provided to the applicants without the necessity of the applicants filing a second Information Disclosure Statement.

In the Information disclosure statement of 29 March 2006, documents 4 and 8 were not provided.

Appropriate corrections are required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Rejection #1 under 35 U.S.C. 102(b):

Claims 2, 3, 12, 55, and 56 are rejected under 35 U.S.C. 102(b) as being anticipated by Ruan et al. [Journal of Dairy Science, volume 81, 1998, pages 9-15] in light of the definition of "Heat map" in Wikipedia [accessed at http://en.wikipedia.org/wiki/Heat_map on 6 December 2006].

Claims 2, 3, 12, 55, and 56 state:

2. A method for presenting analysis of a plurality of individual quantitative lipid metabolite profiles, comprising: designating the plurality of individual quantitative lipid

metabolite profiles; identifying at least one difference or at least one similarity in a lipid metabolite in the plurality of individual quantitative lipid metabolite profiles; and displaying at least one difference or at least one similarity in the lipid metabolite in the plurality of individual quantitative lipid metabolite profiles, wherein the at least one difference or at least one similarity is displayed on a heat map or targeting chart.

3. The method of claim 2, wherein each quantitative lipid metabolite profile comprises quantitative measurements of at least two lipids and wherein the quantified measurements are obtained using an internal standard for at least one of the lipids.

12. The method of claim 2, wherein at least one of the individual quantitative lipid metabolite profiles is generated using a method comprising: separating a biological sample into fractions based on a plurality of lipid classes, wherein at least one quantitative internal standard is included for each lipid class; and measuring the quantity of a plurality of lipid metabolites in the fractions.

55. The method of claim 2, wherein the at least one difference or at least one similarity is displayed on a heat map.

56. The method of claim 55, wherein an increase or decrease in the lipid metabolite is indicated on the heat map by a color and the relevant amount of the increase or decrease is indicated by the intensity of the color.

The study of Ruan et al., entitled, "A magnetic resonance imaging technique for quantitative mapping of moisture and fat in a cheese block," states in the abstract:

> Separate magnetic resonance images of water fat of oil-in-water emulsions and cheese blocks were obtained using the chemical shift selective suppression technique. With this technique, the proton signals emitted from water can be readily separated from those emitted from fat in the same sample through a single experiment using magnetic resonance imaging. Relaxation compensation was made to improve the quality of suppression. The experiment using oil-in-water emulsions demonstrated an excellent linear relationship between the intensity of the signal and the concentration of water or fat.

The Materials and Methods section on the second column of page 10 of Ruan et al. elaborates on the procedures of the method described in the abstract:

> ***Oil-in water-emulsions.*** Oil in water emulsions were prepared to serve as homogeneous samples for the purpose of development and testing of the MRI techniques. The emulsions were freshly made before the MRI experiments by taking known amounts of vegetable oil (Crisco oil; Proctor & Gamble, Cincinnati, OH) with 3 mM CuSO4 in 20 mm diameter glass tubes... Percentages of oil by volume were 0, 20, 30, 40, 50, 60, 70, and 100%. Three percent of Tween 40 (polyoxyethylene sorbitan monooleate) by volume of the oil was added to improve the stability of the mixture.

Once these oil and water emulsions are made, they are used to generate multiple "lipid metabolite profiles" as explained below.

To clarify the definition of "lipid metabolite profiles," metabolites are defined on page 8 of the instant specification as:

> A biomolecule that has a functional and/or compositional role (such as a component of a membrane) in a biological system, and which is not a molecule of DNA, RNA, or protein. Examples of metabolites include lipids, carbohydrates, vitamins, co-factors, pigments, and so forth. Metabolites can be obtained through the diet (consumed from the environment) or synthesized within an organism... By profiling the metabolite composition of a biological sample, for instant using the methods described herein, data on genotype, metabolism, and diet can be obtained in great detail.

Consequently, the language of this definition does not eliminate the possibility that any molecule in a biological system that has a functional or compositional role (that is not DNA, RNA, or protein) is a metabolite. For example, water fits this definition in the instant specification.

Metabolite profiles are defined in the instant specification on page 9, lines 3-5, as:

> The set of data produced from analysis of an individual sample is referred to herein as a individual [sic] lipid profile/metabolic profile ("lipomic profile") of that sample. Certain examples of lipid metabolite profiles include a highly comprehensive set of metabolic measurements (a profile) by multi-parallel analyses.
>
> The comparison of two metabolite profiles of similar scope (i.e. containing information about the same or a similar or overlapping set or subset of metabolites) from cells/tissues/subjects that have been differently treated, or that are genetically different based on disease state or condition, provides information on the metabolic effects of the difference.

As stated in the claims cited above, the language of the instant claims uses "lipid metabolic profiles," which narrows the scope of the invention to metabolic profiles of lipids.

In the section "Imaging and quantification of water and fat in homogenous fat and water phantoms" on page 12 of Ruan et al., Ruan et al. finds two linear equations corresponding to Figures 5A and 5B, respectively, each of which is interpreted as a "lipid metabolic profile."

Figure 5A is the lipid metabolite profile of the oil-in-water emulsions in a water suppressed MRI image while Figure 5B is the lipid metabolite profile of the same set of oil in water emulsions in a fat suppressed image. Equations 1 and 2 quantify the intensities of the lipid metabolite profiles in Figures 5A and 5B, respectively, to reveal the similarity that the two correlations between the concentration of oil (and water) in the binary mixture and image intensity are linear. The cited definitions and claims do not require each "lipid metabolite profile" to be taken from different sets of samples.

In Figure 5B, the concentration of water is measured because the lipids are suppressed in the image. Water is not a lipid, but in a binary mixture of water and oil, the concentration of water is directly and uniquely dependent on the amount of oil added (the volume of the mixture not occupied by water can only be occupied by oil).

Ruan et al. elaborates on this generation of a plurality metabolite profiles generated from the series of oil in water emulsions described above on page 12, column 2:

> Figure 5 shows a series of water suppressed (A) and fat suppressed (B) magnetic resonance images of the oil-in-water emulsion phantoms. Greater brightness indicates a stronger signal. The signal intensities vary as the water and fat contents vary. When signals that were emitted from water were suppressed (Figure 5A), the signal intensity increased as water content increased. When fat or water was absent from the mixture, little signal can be seen in the water-suppressed or fat-suppressed images, indicating that reliable selective signal suppression was achieved... An excellent linear correlation between the MRI signal intensity and water and fat contents was found.

Figure 5 on page 13 of Ruan et al. illustrates a "heat map" of the fat contents of a variety of different lipid composition profiles. The caption to Figure 5 states, "Magnetic resonance images of oil-in-water phantoms: A. water-suppressed images (the percentages indicate the oil contents of the mixtures); B. oil-suppressed images (the percentages indicate the water contents of the mixtures)."

Consequently, Ruan et al. shows analysis of multiple lipid mixtures using magnetic resonance imaging, which are designated and mapped in Figure 5 of Ruan et al.

The term "heat map" is not mentioned in the study of Ruan et al.

The definition of "heat map" in Wikipedia states:

> A heat map is a graphical representation of data where the values taken by a variable in a two-dimensional map are represented as colours.

It is inherent that the illustration in Figure 5 of Ruan et al. is a heat map because it is a two dimensional map of multiple lipid profiles marked by shades of colors.

<u>Rejection #2 under 35 U.S.C. 102(b):</u>

Claims 2, 3, 5, 6, 12, and 54 are rejected under 35 U.S.C. 102(b) as being anticipated by Wong et al. [Magnetic Resonance in Medicine, 1994, volume 32, page 440-446].

Claims 2, 3, 5, 6, 12, and 54 state:

2. A method for presenting analysis of a plurality of individual quantitative lipid metabolite profiles, comprising: designating the plurality of individual quantitative lipid metabolite profiles; identifying at least one difference or at least one similarity in a lipid metabolite in the plurality of individual quantitative lipid metabolite profiles; and displaying at least one difference or at least one similarity in the lipid metabolite in the plurality of individual quantitative lipid metabolite profiles, wherein the at least one

difference or at least one similarity is displayed on a heat map or targeting chart.

3. The method of claim 2, wherein each quantitative lipid metabolite profile comprises quantitative measurements of at least two lipids and wherein the quantified measurements are obtained using an internal standard for at least one of the lipids.

5. The method of claim 2, wherein the quantitative lipid metabolite profiles each comprise a quantified measurement of a lipid in a lipid class.

6. The method of claim 5, wherein the quantified measurement of the lipid in the lipid class is obtained using an internal standard for the lipid class.

12. The method of claim 2, wherein at least one of the individual quantitative lipid metabolite profiles is generated using a method comprising: separating a biological sample into fractions based on a plurality of lipid classes, wherein at least one quantitative internal standard is included for each lipid class; and measuring the quantity of a plurality of lipid metabolites in the fractions.

54. The method of claim 3, wherein the at least one difference of at least one similarity is displayed on a targeting chart.

The article of Wong et al., entitled, "Quantitation of lipid in biological tissue by chemical shift magnetic resonance imaging," states in the abstract:

> A method of combining several previously used approaches is described for the rapid, accurate quantitation of the fat content of biological tissue based on chemical shift images (CSI) corrected for magnetic field inhomogeneity, and compensated for T1 and T2 effects. The gravimetrically determined lipid content of fatty tissues (pork fat, rabbit and human liver) that had been differentially depleted of lipid by chloroform extraction correlated well (r= 0.99) with the lipid image intensities of the respective tissues. This multipoint CSI method was used to quantitate in fresh fatty human tissue (wet and dry) containing varying amounts of lipid. Plots of integrated lipid intensity versus tissue lipid content gave straight parallel lines for hydrated (r= 0.94) and dehydrated (r = 0.98) tissues, permitting determination of a proportionality constant for measuring absolute amounts of lipid present in a specific biological tissue. These results suggest the feasibility of using the method in vivo for absolute quantitation of lipid in tissues of agricultural (e.g. pork, beef) and medical (e.g. human liver) interest.

Metabolite profiles are defined in the instant specification on page 9, lines 3-5, as:

> The set of data produced from analysis of an individual sample is referred to herein as a individual [sic] lipid profile/metabolic profile ("lipomic profile") of that sample. Certain examples of lipid metabolite profiles include a highly comprehensive set of metabolic measurements (a profile) by multi-parallel analyses.

> The comparison of two metabolite profiles of similar scope (i.e. containing information about the same or a similar or overlapping set or subset of metabolites) from cells/tissues/subjects that have been differently treated, or that are genetically different based on disease state or condition, provides information on the metabolic effects of the difference.

Figure 6 on page 465 of Wong et al. illustrates a parity plot comparing several experiments (the equivalent of applicants' "targeting chart").

The caption of Figure 6 of Wong et al. states:

> Lipid image intensity relation to lipid content of fresh (closed triangles) and dehydrated (open circles) human liver tissue. The image intensities (compensated for T1 and T2 effects) indicated on the ordinate scale represent the fraction of the intensity displayed by a 0.8321 g reference of Crisco shortening....

Figure 6 of Wong et al. not only illustrates this "targeting chart," but also plots data relating to image intensities of two tissue types (fresh and dehydrated human liver) as a function of lipid concentration in the tissue. The differences between the slopes and intercepts of the two lines plotted in Figure 6 of Wong et al. represent different imaging properties of the liver tissues used.

Consequently, the abstract of Wong et al. and Figure 6 of Wong et al. teach a plurality of lipid metabolite profiles within animal tissue, and the parity plots (Figure 6) reinforce the differences between the two lipid profiles in comparing the image intensities of both the fresh and dehydrated human liver tissues to the grams of lipid per gram of tissue.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

<u>Rejection #1 under 35 U.S.C. 103(a):</u>

Claims 2 and 57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wong et al. in view of Moser et al. [Neurochemical Research, volume 24, 1999, pages 187-197].

Claim 57 teaches the method of claim 2, further comprising generating a written report.

The article of Wong et al., entitled, "Quantitation of lipid in biological tissue by chemical shift magnetic resonance imaging," states in the abstract:

> A method of combining several previously used approaches is described for the rapid, accurate quantitation of the fat content of biological tissue based on chemical shift images (CSI) corrected for magnetic field inhomogeneity, and compensated for T1 and T2 effects. The gravimetrically determined lipid content of fatty tissues (pork fat, rabbit and human liver) that had been differentially depleted of lipid by chloroform extraction correlated well (r= 0.99) with the lipid image intensities of the respective tissues. This multipoint CSI method was used to quantitate in fresh fatty human tissue (wet and dry) containing varying amounts of lipid. Plots of integrated lipid intensity versus tissue lipid content gave straight parallel lines for hydrated (r= 0.94) and dehydrated (r = 0.98) tissues, permitting determination of a proportionality constant for measuring absolute amounts of lipid present in a specific biological tissue. These results suggest the feasibility of using the method in vivo for absolute quantitation of lipid in tissues of agricultural (e.g. pork, beef) and medical (e.g. human liver) interest.

Metabolite profiles are defined in the instant specification on page 9, lines 3-5, as:

> The set of data produced from analysis of an individual sample is referred to herein as a individual [sic] lipid profile/metabolic profile ("lipomic profile") of that sample. Certain examples of lipid metabolite profiles include a highly comprehensive set of metabolic measurements (a profile) by multi-parallel analyses.

> The comparison of two metabolite profiles of similar scope (i.e. containing information about the same or a similar or overlapping set or subset of metabolites) from cells/tissues/subjects that have been differently treated, or that are genetically different based on disease state or condition, provides information on the metabolic effects of the difference.

Figure 6 on page 465 of Wong et al. illustrates a parity plot comparing several experiments (the equivalent of applicants' "targeting chart").

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Figure 6 of Wong et al. not only illustrates this "targeting chart," but also plots data relating to image intensities of two tissue types (fresh and dehydrated human liver) as a function of lipid concentration in the tissue. The differences between the slopes and intercepts of the two lines plotted in Figure 6 of Wong et al. represent different imaging properties of the liver tissues used.

Consequently, the abstract of Wong et al. and Figure 6 of Wong et al. teach a plurality of lipid metabolite profiles within animal tissue, and the parity plots (Figure 6) reinforce the differences between the two lipid profiles in comparing the image intensities of both the fresh and dehydrated human liver tissues to the grams of lipid per gram of tissue.

However, Wong et al. does not teach listing a written report of the results of the lipid profiles.

The study of Moser et al., entitled, "Plasma and red blood cell fatty acids in peroxisomal disorders," states in the first sentence of the abstract, "The demonstration

of abnormal levels of fatty acids or plasmalogens in plasma or red blood cells is key to the diagnosis of peroxisomal disorders."

In Tables I, III, and IV of Moser et al., written reports of analysis of the plasma in red blood cell samples is listed.

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the lipid composition study of Wong et al. in view of the red blood cell analysis of red blood cells of Moser et al., because while both studies quantify lipids in biological tissues (human liver tissue in Wong et al. and red blood cells in Moser et al.), Moser et al. has the advantage of analyzing lipids in the form of a written report to address peroxisomal disorders.

<u>Rejection #2 under 35 U.S.C. 103(a):</u>

Claims 2, 12, 15, and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wong et al. in view of Moser et al. [Moser et al., Annals of Neurology, volume 45, 1999, pages 100-110]. This reference is referred to throughout this Office action as "Moser et al., (Neurology)."

Claims 15 and 16 limit the method of claim 12 to wherein the separating and measuring methods comprise chromatography.

The article of Wong et al., entitled, "Quantitation of lipid in biological tissue by chemical shift magnetic resonance imaging," states in the abstract:

> A method of combining several previously used approaches is described for the rapid, accurate quantitation of the fat content of biological tissue based on chemical shift images (CSI) corrected for magnetic field inhomogeneity, and compensated for T1 and T2 effects. The gravimetrically determined lipid content of fatty tissues (pork fat, rabbit and human liver) that had been differentially depleted of lipid by chloroform extraction correlated well (r= 0.99) with the lipid image

> intensities of the respective tissues. This multipoint CSI method was used to quantitate in fresh fatty human tissue (wet and dry) containing varying amounts of lipid. Plots of integrated lipid intensity versus tissue lipid content gave straight parallel lines for hydrated (r= 0.94) and dehydrated (r = 0.98) tissues, permitting determination of a proportionality constant for measuring absolute amounts of lipid present in a specific biological tissue. These results suggest the feasibility of using the method in vivo for absolute quantitation of lipid in tissues of agricultural (e.g. pork, beef) and medical (e.g. human liver) interest.

Metabolite profiles are defined in the instant specification on page 9, lines 3-5, as:

> The set of data produced from analysis of an individual sample is referred to herein as a individual [sic] lipid profile/metabolic profile ("lipomic profile") of that sample. Certain examples of lipid metabolite profiles include a highly comprehensive set of metabolic measurements (a profile) by multi-parallel analyses.
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> The comparison of two metabolite profiles of similar scope (i.e. containing information about the same or a similar or overlapping set or subset of metabolites) from cells/tissues/subjects that have been differently treated, or that are genetically different based on disease state or condition, provides information on the metabolic effects of the difference.

Figure 6 on page 465 of Wong et al. illustrates a parity plot comparing several experiments (the equivalent of applicants' "targeting chart").

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Figure 6 of Wong et al. not only illustrates this "targeting chart," but also plots data relating to image intensities of two tissue types (fresh and dehydrated human liver) as a function of lipid concentration in the tissue. The differences between the slopes and intercepts of the two lines plotted in Figure 6 of Wong et al. represent different imaging properties of the liver tissues used.

Consequently, the abstract of Wong et al. and Figure 6 of Wong et al. teach a plurality of lipid metabolite profiles within animal tissue,.and the parity plots (Figure 6)

reinforce the differences between the two lipid profiles in comparing the image intensities of both the fresh and dehydrated human liver tissues to the grams of lipid per gram of tissue.

However, Wong et al. does not teach chromatography.

The study of Moser et al. (Neurology), entitled, "Plasma very long chain fatty acids in 3,000 peroxisome disease patients and 29,000 controls," states in the first sentence of the abstract, "The assay of plasma very long chain fatty acids (VLCFAs), developed in our laboratory on 1981, has become the most widely used procedure for the diagnosis of X-linked adrenoleukodystrophy (X-ALD) and other peroxisomal disorders."

The second column of page 101 of Moser et al. (Neurology) states:

> *Capillary Gas Liquid Chromatographic Analysis of Very Long Chain Fatty Acids*
> The VLCFA assay procedure was described in 1981 and modified in 1991. Recently we have introduces a two-column procedure that permits quantitation of 65 fatty acids. All three procedures give identical results for three measurements that are the topic of the present report.

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the lipid composition study of Wong et al. in view of the chromatographic analysis of Moser et al. (Neurology), because while both studies quantify lipids in biological tissues (human liver tissue in Wong et al. and blood in Moser et al. (Neurology)), Moser (Neurology) has the advantage of using chromatographic analysis of lipids to address peroxisomal disorders.

Rejection #3 under 35 U.S.C. 103(a):

Claims 2, 3, 6, 7, 9, 12 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wong et al. in view of Watkins et al. [Journal of Lipid Research, volume 39, 1998, pages 1583-1588].

Claims 7, 9, and 13 state (elected species in italics):

7. The method of claim 5, wherein the lipid is selected from the group consisting of fatty acid 16:0, 18:0, 16:1n7; 18:1n7; 18:1n9; 18:3n3; 20:5n3; 22:5n3; 22:6n3; ***18:2n6***; 18:3n6; 20:3n6; and 20:4n6.

9. The method of claim 5, wherein the lipid class is selected from the group consisting of lyso-phosphatidylcholine, sphingomyelin, phosphatidylcholine, phosphatidylserine, phosphatidylinositol, phosphatidylethanolamine, ***cardiolipin***, free fatty acids, monoacylglycerides, diacylglycerides, triacylglycerides, and cholesterol esters.

13. The method of claim 12, wherein the plurality of lipid classes comprises lyso-phosphatidylcholines, sphingomyelins, phosphatidylcholines, phosphatidylserines, phosphatidylinositols, phosphatidylethanolamines, ***cardiolipins***, free fatty acids, monoacylglycerides, diacylglycerides, triacylglycerides, or cholesterol esters.

The article of Wong et al., entitled, "Quantitation of lipid in biological tissue by chemical shift magnetic resonance imaging," states in the abstract:

> A method of combining several previously used approaches is described for the rapid, accurate quantitation of the fat content of biological tissue based on chemical shift images (CSI) corrected for magnetic field inhomogeneity, and compensated for T1 and T2 effects. The gravimetrically determined lipid content of fatty tissues (pork fat, rabbit and human liver) that had been differentially depleted of lipid by chloroform extraction correlated well (r= 0.99) with the lipid image intensities of the respective tissues. This multipoint CSI method was used to quantitate in fresh fatty human tissue (wet and dry) containing varying amounts of lipid. Plots of integrated lipid intensity versus tissue lipid content gave straight parallel lines for hydrated (r= 0.94) and dehydrated (r = 0.98) tissues, permitting determination of a proportionality constant for measuring absolute amounts of lipid present in a specific biological tissue. These results suggest the feasibility of using the method in vivo for absolute quantitation of lipid in tissues of agricultural (e.g. pork, beef) and medical (e.g. human liver) interest.

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> The set of data produced from analysis of an individual sample is referred to herein as a individual [sic] lipid profile/metabolic profile ("lipomic profile") of that sample. Certain examples of lipid metabolite profiles include a highly comprehensive set of metabolic measurements (a profile) by multi-parallel analyses.
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Consequently, the abstract of Wong et al. and Figure 6 of Wong et al. teach a plurality of lipid metabolite profiles within animal tissue, and the parity plots (Figure 6) reinforce the differences between the two lipid profiles in comparing the image intensities of both the fresh and dehydrated human liver tissues to the grams of lipid per gram of tissue.

However, Wong et al. does not teach use of cardiolipins and specifically the linoleic acid 18:2 n-6.

The study of Watkins et al., entitled, "Docosahexaxenoic acid accumulates in cardiolipin and enhances HT-29 cell oxidant production," states in the first sentence of the abstract, "The objective of this study was to investigate membrane fatty acids for their effects on mitochondrial function in live cells."

The top of column 2 of page 1583 details some of the specific lipid studied, as stated, "In mammals, CL acyl composition is unusually sensitive to diet, and in humans it is rich in the essential fatty acid linoleic acid (LA, 18:2 n-6)."

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the lipid composition study of Wong et al. in view of the cardiolipin study of Watkins et al., because while both studies quantify lipids in biological tissues (human liver tissue in Wong et al. and cardiolipins in mitochondria in Watkins et al.), Watkins et al. has the advantage of quantifying cardiolipins in mitochondria for the purpose of understanding oxidant production and aging.

<u>Rejection #4 under 35 U.S.C. 103(a):</u>

Claims 2-4, 12, and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wong et al. in view of Watkins et al. as applied to claims 2, 3, 6, 7, 9, 12 and 13, above, in further view of Siguel [US Patent 5,075,101; IDS of 1/5/2004] as evidenced by the definition of eicosapentaenoic acid (EPA) [www.pdrhealth.com, accessed 6 December 2006].

Claims 4 and 14 state (elected species in italics):

4. The method of claim 3, wherein the lipid metabolites are selected from the group consisting of tetradecanoic acid, pentadecanoic acid, hexadecanoic acid,

heptadecanoic acid, octadecanoic acid, eicosanoic acid, docosanoic acid, tetracosanoic acid, 9-tetradecenoic acid, 9-hexadecenoic acid, 11-octadecenoic acid, 9-octadecenoic acid, 11-eicosenoic acid, ***5,8,11-eicosatrienoic acid***, 13-docosenoic acid, 15-tetracosenoic acid, 9,12,15-octadecatrienoic acid, 6,9,12,15-octadecatetraenoic acid, 11,14,17-eicosatrienoic acid, 8,11,14,17-eicosictetraenoic acid, ***5,8,11,14,17-eicosapentaenoic acid,*** 7,10,13,16,19-docosapentaenoic acid, 4,7,10,13,16,19-docosahexaenoic acid, 6,9,12,15,18,21-tetracoshexaenoic acid, 9,12-octadecadienoic acid, 6,9,12-octadecatrienoic acid, 11,14-eicosadienoic acid, 8,11,14-eicosatrienoic acid, 5,8,11,14-eicosicatetraenoic acid, 13,16-docsadienoic acid, 7,10,13,16-docosicatetraenoic acid, 4,7,10,13,16-docosapentaenoic acid, 9-trans-hexadecenoic acid, 9-trans-octadecenoic acid, 8-eicosaenoic acid, 5-eicosaenoic acid, plasmalogen fatty acids, 5b-cholestan-3b-ol, 5a-cholestan-3b-ol, 5-cholesten-3b-ol, 5,24-cholestadien-3b-ol, 5-cholestan-25a-methyl-3b-ol, 5-cholestan-24b-methyl-3b-ol, 5-cholesten-24b-ethyl-3b-ol, and 5,22-cholestadien-24b-ethyl-3b-ol, each as a compound or a component of a lipid molecule.

14. The method of claim 12, wherein the plurality of lipid metabolites comprises at least one of tetradecanoic acid, pentadecanoic acid, hexadecanoic acid, heptadecanoic acid, octadecanoic acid, eicosanoic acid, docosanoic acid, tetracosanoic acid, 9-tetradecenoic acid, 9-hexadecenoic acid, 11-octadecenoic acid, 9-octadecenoic acid, 11-eicosenoic acid, ***5,8,11-eicosatrienoic acid***, 13-docosenoic acid, 15-tetracosenoic acid, 9,12,15-octadecatrienoic acid, 6,9,12,15-octadecatetraenoic acid, 11,14,17-eicosatrienoic acid, 8,11,14,17-eicosictetraenoic acid, ***5,8,11,14,17-eicosapentaenoic acid***, 7,10,13,16,19-docosapentaenoic acid, 4,7,10,13,16,19-docosahexaenoic acid, 6,9,12,15,18,21-tetracoshexaenoic acid, 9,12-octadecadienoic acid, 6,9,12-octadecatrienoic acid, 11,14-eicosadienoic acid, 8,11,14-eicosatrienoic acid, 5,8,11,14-eicosicatetraenoic acid, 13,16-docsadienoic acid, 7,10,13,16-docosicatetraenoic acid, 4,7,10,13,16-docosapentaenoic acid, 9-trans-hexadecenoic acid, 9-trans-octadecenoic acid, 8-eicosaenoic acid, 5-eicosaenoic acid, plasmalogen fatty acids, 5b-cholestan-3b-ol, 5a-cholestan-3b-ol, 5-cholesten-3b-ol, 5,24-cholestadien-3b-ol, 5-cholestan-25a-methyl-3b-ol, 5-cholestan-24b-methyl-3b-ol, 5-cholesten-24b-ethyl-3b-ol, or 5,22-cholestadien-24b-ethyl-3b-ol, each as a compound or a component of a lipid molecule.

While Wong et al. in view of Watkins et al. teach the method of fatty acid analysis of cells, including EPA, they do not teach the specific nomenclature of the claim required in claim language. Additionally, the above mentioned prior art does not teach 5,8,11-eicosatrienoic acid (Mead acid).

The web site [www.pdrhealth.com] clarifies the nomenclature and structure of EPA as 5,8,11,14,17-eicosapentaenoic acid.

The patent of Siguel, entitled, “Method of diagnosis of fatty acid or lipid abnormalities,” states in column 3, lines 55-65, that Mead acid is an essential fatty acid important in preventing essential fatty acid deficiency.

It would have been obvious for someone of ordinary skill in the art at the time of the instant invention to practice Wong et al. in view of Watkins et al. as applied to claims 2, 3, 6, 7, 9, 12, and 13 above, in further view of Siguel as evidenced by the definition of EPA because Siguel shows the advantage of Mead acid in that adequate amounts of Mead acid are required to prevent lipid deficiency in the blood.

Rejection #5 under 35 U.S.C. 103(a):

Claims 2, 17, and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wong et al. in view of “The World of Membrane Lipids,” [www.biochem.Missouri.edu/~lesa/LIPIDS/membrane_lipid.html; accessed on 6 December 2006, page made on 2 February 1999].

Claim 17 claims the method of claim 2, wherein displaying generates a web page for viewing.

Claim 19 limits claim 17 wherein the web page comprises a targeting chart.

The article of Wong et al., entitled, “Quantitation of lipid in biological tissue by chemical shift magnetic resonance imaging,” states in the abstract:

> A method of combining several previously used approaches is described for the rapid, accurate quantitation of the fat content of biological tissue based on chemical shift images (CSI) corrected for magnetic field inhomogeneity, and compensated for T1 and T2 effects. The gravimetrically determined lipid content of fatty tissues (pork fat, rabbit and human liver) that had been differentially depleted of lipid by chloroform extraction correlated well (r= 0.99) with the lipid image intensities of the respective tissues. This multipoint CSI method was used to quantitate in fresh fatty human tissue (wet and dry) containing varying amounts of lipid. Plots of integrated lipid

> intensity versus tissue lipid content gave straight parallel lines for hydrated (r= 0.94) and dehydrated (r = 0.98) tissues, permitting determination of a proportionality constant for measuring absolute amounts of lipid present in a specific biological tissue. These results suggest the feasibility of using the method in vivo for absolute quantitation of lipid in tissues of agricultural (e.g. pork, beef) and medical (e.g. human liver) interest.

Metabolite profiles are defined in the instant specification on page 9, lines 3-5, as:

> The set of data produced from analysis of an individual sample is referred to herein as a individual [sic] lipid profile/metabolic profile ("lipomic profile") of that sample. Certain examples of lipid metabolite profiles include a highly comprehensive set of metabolic measurements (a profile) by multi-parallel analyses.
>
> The comparison of two metabolite profiles of similar scope (i.e. containing information about the same or a similar or overlapping set or subset of metabolites) from cells/tissues/subjects that have been differently treated, or that are genetically different based on disease state or condition, provides information on the metabolic effects of the difference.

Figure 6 on page 465 of Wong et al. illustrates a parity plot comparing several experiments (the equivalent of applicants' "targeting chart").

The caption of Figure 6 of Wong et al. states:

> Lipid image intensity relation to lipid content of fresh (closed triangles) and dehydrated (open circles) human liver tissue. The image intensities (compensated for T1 and T2 effects) indicated on the ordinate scale represent the fraction of the intensity displayed by a 0.8321 g reference of Crisco shortening....

Figure 6 of Wong et al. not only illustrates this "targeting chart," but also plots data relating to image intensities of two tissue types (fresh and dehydrated human liver) as a function of lipid concentration in the tissue. The differences between the slopes and intercepts of the two lines plotted in Figure 6 of Wong et al. represent different imaging properties of the liver tissues used.

Consequently, the abstract of Wong et al. and Figure 6 of Wong et al. teach a plurality of lipid metabolite profiles within animal tissue, and the parity plots (Figure 6) reinforce the differences between the two lipid profiles in comparing the image

intensities of both the fresh and dehydrated human liver tissues to the grams of lipid per gram of tissue.

However, Wong et al. do not teach the use of a web page for electronically displaying of results.

"The World of Membrane Lipids," states in its introduction:

> This website is an unofficial home for membrane lipid crystal structures. Here, you'll be able to find information about the nomenclature, crystallization, etc. of membrane lipids. Although about 50 structures are known, most of them are not in a database, so the only source of their coordinates is the original journal article.
> The purpose of this site is to make this information available to anyone interested, especially structural biologists. To facilitate their use, all coordinate files are in PDB format. If you have any comments or contributions, please send them to Lesa Beamer.

It would be obvious to someone of ordinary skill in the art at the time of the instant invention to modify the lipid quantification method of Wong et al. in view of the web posting database of "The World of Membrane Lipids," because posting lipid results on a web page has the advantage of making the data available to the general public.

<u>Rejection #6 under 35 U.S.C. 103(a):</u>

Claims 2, 17, and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ruan et al. in view of "The World of Membrane Lipids," [www.biochem.Missouri.edu/~lesa/LIPIDS/membrane_lipid.html; accessed on 6 December 2006, page made on 2 February 1999] as evidenced by the definition of "Heat map" in Wikipedia.

Claim 17 claims the method of claim 2, wherein displaying generates a web page for viewing.

The study of Ruan et al., entitled, "A magnetic resonance imaging technique for quantitative mapping of moisture and fat in a cheese block," states in the abstract:

> Separate magnetic resonance images of water fat of oil-in-water emulsions and cheese blocks were obtained using the chemical shift selective suppression technique. With this technique, the proton signals emitted from water can be readily separated from those emitted from fat in the same sample through a single experiment using magnetic resonance imaging. Relaxation compensation was made to improve the quality of suppression. The experiment using oil-in-water emulsions demonstrated an excellent linear relationship between the intensity of the signal and the concentration of water or fat.

The Materials and Methods section on the second column of page 10 of Ruan et al. elaborates on the procedures of the method described in the abstract:

> ***Oil-in water-emulsions***. Oil in water emulsions were prepared to serve as homogeneous samples for the purpose of development and testing of the MRI techniques. The emulsions were freshly made before the MRI experiments by taking known amounts of vegetable oil (Crisco oil; Proctor & Gamble, Cincinnati, OH) with 3 mM CuSO4 in 20 mm diameter glass tubes... Percentages of oil by volume were 0, 20, 30, 40, 50, 60, 70, and 100%. Three percent of Tween 40 (polyoxyethylene sorbitan monooleate) by volume of the oil was added to improve the stability of the mixture.

Once these oil and water emulsions are made, they are used to generate multiple "lipid metabolite profiles" as explained below.

To clarify the definition of "lipid metabolite profiles," metabolites are defined on page 8 of the instant specification as:

> A biomolecule that has a functional and/or compositional role (such as a component of a membrane) in a biological system, and which is not a molecule of DNA, RNA, or protein. Examples of metabolites include lipids, carbohydrates, vitamins, co-factors, pigments, and so forth. Metabolites can be obtained through the diet (consumed from the environment) or synthesized within an organism... By profiling the metabolite composition of a biological sample, for instant using the methods described herein, data on genotype, metabolism, and diet can be obtained in great detail.

Consequently, the language of this definition does not eliminate the possibility that any molecule in a biological system that has a functional or compositional role (that is not DNA, RNA, or protein) is a metabolite. For example, water fits this definition in the instant specification.

Metabolite profiles are defined in the instant specification on page 9, lines 3-5, as:

> The set of data produced from analysis of an individual sample is referred to herein as a individual [sic] lipid profile/metabolic profile ("lipomic profile") of that sample. Certain examples of lipid metabolite profiles include a highly comprehensive set of metabolic measurements (a profile) by multi-parallel analyses.
>
> The comparison of two metabolite profiles of similar scope (i.e. containing information about the same or a similar or overlapping set or subset of metabolites) from cells/tissues/subjects that have been differently treated, or that are genetically different based on disease state or condition, provides information on the metabolic effects of the difference.

As stated in the claims cited above, the language of the instant claims uses "lipid metabolic profiles," which narrows the scope of the invention to metabolic profiles of lipids.

In the section "Imaging and quantification of water and fat in homogenous fat and water phantoms" on page 12 of Ruan et al., Ruan et al. finds two linear equations corresponding to Figures 5A and 5B, respectively, each of which is interpreted as a "lipid metabolic profile."

Figure 5A is the lipid metabolite profile of the oil-in-water emulsions in a water suppressed MRI image while Figure 5B is the lipid metabolite profile of the same set of oil in water emulsions in a fat suppressed image. Equations 1 and 2 quantify the intensities of the lipid metabolite profiles in Figures 5A and 5B, respectively, to reveal the similarity that the two correlations between the concentration of oil (and water) in the binary mixture and image intensity are linear. The cited definitions and claims do not require each "lipid metabolite profile" to be taken from different sets of samples.

In Figure 5B, the concentration of water is measured because the lipids are suppressed in the image. Water is not a lipid, but in a binary mixture of water and oil,

the concentration of water is directly and uniquely dependent on the amount of oil added (the volume of the mixture not occupied by water can only be occupied by oil).

Ruan et al. elaborates on this generation of a plurality metabolite profiles generated from the series of oil in water emulsions described above on page 12, column 2:

> Figure 5 shows a series of water suppressed (A) and fat suppressed (B) magnetic resonance images of the oil-in-water emulsion phantoms. Greater brightness indicates a stronger signal. The signal intensities vary as the water and fat contents vary. When signals that were emitted from water were suppressed (Figure 5A), the signal intensity increased as water content increased. When fat or water was absent from the mixture, little signal can be seen in the water-suppressed or fat-suppressed images, indicating that reliable selective signal suppression was achieved... An excellent linear correlation between the MRI signal intensity and water and fat contents was found.

Figure 5 on page 13 of Ruan et al. illustrates a "heat map" of the fat contents of a variety of different lipid composition profiles. The caption to Figure 5 states, "Magnetic resonance images of oil-in-water phantoms: A. water-suppressed images (the percentages indicate the oil contents of the mixtures); B. oil-suppressed images (the percentages indicate the water contents of the mixtures)."

Consequently, Ruan et al. shows analysis of multiple lipid mixtures using magnetic resonance imaging, which are designated and mapped in Figure 5 of Ruan et al.

The term "heat map" is not mentioned in the study of Ruan et al.

The definition of "heat map" in Wikipedia states:

> A heat map is a graphical representation of data where the values taken by a variable in a two-dimensional map are represented as colours.

It is inherent that the illustration in Figure 5 of Ruan et al. is a heat map because it is a two dimensional map of multiple lipid profiles marked by shades of colors.

However, Ruan et al. do not teach the use of a web page for electronically displaying of results.

"The World of Membrane Lipids," states in its introduction:

> This website is an unofficial home for membrane lipid crystal structures. Here, you'll be able to find information about the nomenclature, crystallization, etc. of membrane lipids. Although about 50 structures are known, most of them are not in a database, so the only source of their coordinates is the original journal article.
> The purpose of this site is to make this information available to anyone interested, especially structural biologists. To facilitate their use, all coordinate files are in PDB format. If you have any comments or contributions, please send them to Lesa Beamer.

It would be obvious to someone of ordinary skill in the art at the time of the instant invention to modify the lipid quantification method of Ruan et al. as evidenced by the definition of "Heat map" in view of the web posting database of "The World of Membrane Lipids," because posting lipid results on a web page has the advantage of making the data available to the general public.

Rejection #7 under 35 U.S.C. 103(a):

Claims 2 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wong et al. in view of Grav et al. [Journal of Chromatography B, volume 658, 1994, pages 1-10].

Claim 10 states:

10. The method of claim 6, wherein the internal standard is selected from the group consisting of diheptadecanoyl phosphatidylcholine, dipentadecaenoyl phosphatidylethanolamine, tetraheptadecenoyl cardiolipin, diheptadecenoyl phosphatidylserine, pentadecenoyl sphingomyelin, heptadecanoyl lyso-phosphatidylcholine, tripheptadecaenoyl glyceride, pentadecaenoic acid, heptadecanoic cholesterol ester and free fucosterol.

The article of Wong et al., entitled, "Quantitation of lipid in biological tissue by chemical shift magnetic resonance imaging," states in the abstract:

> A method of combining several previously used approaches is described for the rapid, accurate quantitation of the fat content of biological tissue based on chemical shift images (CSI) corrected for magnetic field inhomogeneity, and compensated for T1 and T2 effects. The gravimetrically determined lipid content of fatty tissues (pork fat, rabbit and human liver) that had been differentially depleted of lipid by chloroform extraction correlated well (r= 0.99) with the lipid image intensities of the respective tissues. This multipoint CSI method was used to quantitate in fresh fatty human tissue (wet and dry) containing varying amounts of lipid. Plots of integrated lipid intensity versus tissue lipid content gave straight parallel lines for hydrated (r= 0.94) and dehydrated (r = 0.98) tissues, permitting determination of a proportionality constant for measuring absolute amounts of lipid present in a specific biological tissue. These results suggest the feasibility of using the method in vivo for absolute quantitation of lipid in tissues of agricultural (e.g. pork, beef) and medical (e.g. human liver) interest.

Metabolite profiles are defined in the instant specification on page 9, lines 3-5, as:

> The set of data produced from analysis of an individual sample is referred to herein as a individual [sic] lipid profile/metabolic profile ("lipomic profile") of that sample. Certain examples of lipid metabolite profiles include a highly comprehensive set of metabolic measurements (a profile) by multi-parallel analyses.
>
> The comparison of two metabolite profiles of similar scope (i.e. containing information about the same or a similar or overlapping set or subset of metabolites) from cells/tissues/subjects that have been differently treated, or that are genetically different based on disease state or condition, provides information on the metabolic effects of the difference.

Figure 6 on page 465 of Wong et al. illustrates a parity plot comparing several experiments (the equivalent of applicants' "targeting chart").

The caption of Figure 6 of Wong et al. states:

> Lipid image intensity relation to lipid content of fresh (closed triangles) and dehydrated (open circles) human liver tissue. The image intensities (compensated for T1 and T2 effects) indicated on the ordinate scale represent the fraction of the intensity displayed by a 0.8321 g reference of Crisco shortening....

Figure 6 of Wong et al. not only illustrates this "targeting chart," but also plots data relating to image intensities of two tissue types (fresh and dehydrated human liver) as a function of lipid concentration in the tissue. The differences between the slopes

and intercepts of the two lines plotted in Figure 6 of Wong et al. represent different imaging properties of the liver tissues used.

Consequently, the abstract of Wong et al. and Figure 6 of Wong et al. teach a plurality of lipid metabolite profiles within animal tissue, and the parity plots (Figure 6) reinforce the differences between the two lipid profiles in comparing the image intensities of both the fresh and dehydrated human liver tissues to the grams of lipid per gram of tissue.

The article of Grav et al., entitled, "Gas chromatographic measurement of 3- and 4-thia fatty acids incorporated into various classes of rat liver lipids during feeding experiments," states in the first sentence of the abstract, "A practical procedure is described for the quantitative measurement of the amount of acyl units derived from tetradecylthioacetic acid (effecting hypolipemia in rats) and tetradecylthiopropionic acid (effecting hyperlipemia)."

The abstract of Grav et al. continues, "The overall recoveries of heptadecanoyl lipids added as internal standards using extraction were 94% to 96%, except for cholesteryl heptadecanoate…"

In Grav et al., section 2.3 on page 2, Grav et al. disclose that one of the species used in claim 10, diheptadecanoyl phosphatidylcholine is used as an internal standard.

It would be obvious to someone of ordinary skill in the art at the time of the instant invention to modify the lipid quantification method of Wong et al. in view of the use of standards in lipid quantification of Grav et al. because while both Wong et al. and Grav et al. disclose a method of quantifying lipids in livers, Grav et al. has the

advantage of using the required internal standards in a direct health application in examining hypolipemia and hyperlipemia.

Rejection #8 under 35 U.S.C. 103(a):

Claims 2, 5, and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wong et al. in view of Dutta et al. [JAOCS, volume 74, no. 6, 1997, pages 647-657].

Claim 8 states:

8. The method of claim 5, wherein the lipid is a sterol selected from the group consisting of 5b-cholestan-3b-ol, 5a-cholestan-3b-ol, 5-cholesten-3b-ol, 5,24-cholestadien-3b-ol, 5-cholestan-25a-methyl-3b-ol, 5-cholestan-24b-methyl-3b-ol, 5-cholesten-24b-ethyl-3b-ol, and 5,22-cholestadien-24b-ethyl-3b-ol.

The article of Wong et al., entitled, "Quantitation of lipid in biological tissue by chemical shift magnetic resonance imaging," states in the abstract:

> A method of combining several previously used approaches is described for the rapid, accurate quantitation of the fat content of biological tissue based on chemical shift images (CSI) corrected for magnetic field inhomogeneity, and compensated for T1 and T2 effects. The gravimetrically determined lipid content of fatty tissues (pork fat, rabbit and human liver) that had been differentially depleted of lipid by chloroform extraction correlated well (r= 0.99) with the lipid image intensities of the respective tissues. This multipoint CSI method was used to quantitate in fresh fatty human tissue (wet and dry) containing varying amounts of lipid. Plots of integrated lipid intensity versus tissue lipid content gave straight parallel lines for hydrated (r= 0.94) and dehydrated (r = 0.98) tissues, permitting determination of a proportionality constant for measuring absolute amounts of lipid present in a specific biological tissue. These results suggest the feasibility of using the method in vivo for absolute quantitation of lipid in tissues of agricultural (e.g. pork, beef) and medical (e.g. human liver) interest.

Metabolite profiles are defined in the instant specification on page 9, lines 3-5, as:

> The set of data produced from analysis of an individual sample is referred to herein as a individual [sic] lipid profile/metabolic profile ("lipomic profile") of that sample. Certain examples of lipid metabolite profiles include a highly comprehensive set of metabolic measurements (a profile) by multi-parallel analyses.

> The comparison of two metabolite profiles of similar scope (i.e. containing information about the same or a similar or overlapping set or subset of metabolites) from cells/tissues/subjects that have been differently treated, or that are genetically different based on disease state or condition, provides information on the metabolic effects of the difference.

Figure 6 on page 465 of Wong et al. illustrates a parity plot comparing several experiments (the equivalent of applicants' "targeting chart").

The caption of Figure 6 of Wong et al. states:

> Lipid image intensity relation to lipid content of fresh (closed triangles) and dehydrated (open circles) human liver tissue. The image intensities (compensated for T1 and T2 effects) indicated on the ordinate scale represent the fraction of the intensity displayed by a 0.8321 g reference of Crisco shortening....

Figure 6 of Wong et al. not only illustrates this "targeting chart," but also plots data relating to image intensities of two tissue types (fresh and dehydrated human liver) as a function of lipid concentration in the tissue. The differences between the slopes and intercepts of the two lines plotted in Figure 6 of Wong et al. represent different imaging properties of the liver tissues used.

Consequently, the abstract of Wong et al. and Figure 6 of Wong et al. teach a plurality of lipid metabolite profiles within animal tissue, and the parity plots (Figure 6) reinforce the differences between the two lipid profiles in comparing the image intensities of both the fresh and dehydrated human liver tissues to the grams of lipid per gram of tissue.

However, Wong et al. does not teach use of cholestan-3b-ols.

The article of Dutta et al., entitled, "Studies of phytosterol oxides: I: Effect of storage on the content in potato chips prepared in different vegetable oils," states in the abstract:

> Potato chips fried in palm oil, sunflower oil, and high-oleic sunflower oil were studies for the content of different phytosterol oxides during 0 to 25 weeks of storage in the dark. Oxidation products of sitosterol (2,4 alpha-ethyl-5-cholesten-2b-ol) and campesterol (2,4 alpha methyl-5cholesten-3b-ol) were synthesized to help identify the phytesterol oxides.

Dutta et al. continue in the introduction to explain in the first sentence of the introduction:

> Abundant information exists on the formation of cholesterol oxidation products in foods and their biological implications, but there is relatively little on such products generated from phytosterols.

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the lipid quantification method of Wong et al. in view of the phytosterol quantitation method of Dutta et al. because the study of Dutta et al. has the advantage of using the required fatty acids for further understanding of biological implications of cholesterols and phytosterols.

Conclusion

No claim is allowed.

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the central PTO Fax Center. The faxing of such pages must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CFR § 1.6(d)). The Central PTO Fax Center Number is (571) 273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Russell Negin, Ph.D., whose telephone number is (571) 272-1083. The examiner can normally be reached on Monday-Friday from 7am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's Supervisor, Andrew Wang, Supervisory Patent Examiner, can be reached at (571) 272-0811.

Any inquiry of a general nature or relating to the status of this application should be directed to Legal Instrument Examiner, Yolanda Chadwick, whose telephone number is (571) 272-0514.

Information regarding the status of the application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information on the PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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11 December 2006

11 December 2006

11 December 2006

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PRIMARY EXAMINER